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|---|--|---|--------------------------------------|
| FORM PTO-1390<br>(REV 12-29-99)   |  | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE             | ATTORNEY'S DOCKET NUMBER<br>2635US0P |
| <b>TRANSMITTAL LETTER TO THE UNITED STATES<br/>DESIGNATED/ELECTED OFFICE (DO/EO/US)<br/>CONCERNING A FILING UNDER 35 U.S.C. 371</b>   |  | U.S. APPLICATION NO. (If known, see 37 CFR 1.5)<br><b>09/674624</b> |                                      |
| INTERNATIONAL APPLICATION NO.<br>PCT/JP00/03881   | INTERNATIONAL FILING DATE<br>June 15, 2000 | PRIORITY DATE CLAIMED<br>June 17, 1999                              |                                      |
| TITLE OF INVENTION<br>Benzimidazole Compound Crystal  |  |   |                                      |
| APPLICANT(S) FOR DO/EO/US<br>Akira FUJISHIMA et al.   |  |   |                                      |
| <p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ul style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) * <ul style="list-style-type: none"> <li>a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ul> </li> <li>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ul> </li> <li>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ul> |  |   |                                      |
| <p><b>Items 11. to 16. below concern document(s) or information included:</b></p> <ul style="list-style-type: none"> <li>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <ul style="list-style-type: none"> <li><input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> </ul> </li> <li>14. <input type="checkbox"/> A substitute specification.</li> <li>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>16. <input checked="" type="checkbox"/> Other items or information: <b>A copy of PCT Request (Form PCT/RO/101)</b></li> </ul>  |  |   |                                      |

\* This includes Specification 29 total pages, including  
Claims 1-7 (1 page) and Abstract (1 page).

| U.S. APPLICATION NO. (known, see 37 CFR 1.5) <b>09/674624</b>   | INTERNATIONAL APPLICATION NO.<br>PCT/JP00/03881 | ATTORNEY'S DOCKET NUMBER<br>2635US0P |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
|---|---|--------------------------------------|-------------------|--------------|------|--------------|----------|---|------------------|--------------------|---------|---|------------------|---|--|--|-------------------|------------------|
| <p>17. <input checked="" type="checkbox"/> The following fees are submitted:</p> <p><b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5) ):</b></p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... <b>\$970.00</b></p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$860.00</b></p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$690.00</b></p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$670.00</b></p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$96.00</b></p> |   | <b>CALCULATIONS PTO USE ONLY</b>     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>   |   | <b>\$ 860.00</b>                     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</p>   |   | <b>\$</b>                            |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">CLAIMS</th> <th style="width: 25%;">NUMBER FILED</th> <th style="width: 25%;">NUMBER EXTRA</th> <th style="width: 25%;">RATE</th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>7 - 20 =</td> <td>0</td> <td>X <b>\$18.00</b></td> </tr> <tr> <td>Independent claims</td> <td>2 - 3 =</td> <td>0</td> <td>X <b>\$80.00</b></td> </tr> <tr> <td colspan="2" style="text-align: center;">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td></td> <td>+ <b>\$260.00</b></td> </tr> </tbody> </table>  |   | CLAIMS                               | NUMBER FILED      | NUMBER EXTRA | RATE | Total claims | 7 - 20 = | 0 | X <b>\$18.00</b> | Independent claims | 2 - 3 = | 0 | X <b>\$80.00</b> | MULTIPLE DEPENDENT CLAIM(S) (if applicable) |  |  | + <b>\$260.00</b> | <b>\$ 860.00</b> |
| CLAIMS  | NUMBER FILED                                    | NUMBER EXTRA                         | RATE              |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| Total claims  | 7 - 20 =  | 0                                    | X <b>\$18.00</b>  |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| Independent claims  | 2 - 3 =   | 0                                    | X <b>\$80.00</b>  |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable)   |   |                                      | + <b>\$260.00</b> |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p style="text-align: center;"><b>TOTAL OF ABOVE CALCULATIONS =</b></p>   |   | <b>\$ 860.00</b>                     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).</p>   |   | <b>\$</b>                            |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p style="text-align: center;"><b>SUBTOTAL =</b></p>  |   | <b>\$ 860.00</b>                     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</p>  |   | <b>\$</b>                            |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p style="text-align: center;"><b>TOTAL NATIONAL FEE =</b></p>  |   | <b>\$ 860.00</b>                     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property</p>  |   | <b>\$ 40.00</b>                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p style="text-align: center;"><b>TOTAL FEES ENCLOSED =</b></p>   |   | <b>\$ 900.00</b>                     |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <input type="checkbox"/> <b>Amount to be refunded:</b> <b>\$</b><br><input type="checkbox"/> <b>charged:</b> <b>\$</b>  |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>a. <input type="checkbox"/> A check in the amount of <b>\$</b> _____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <b>500799</b> in the amount of <b>\$ 900.00</b> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <b>500799</b>. A duplicate copy of this sheet is enclosed.</p>   |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b></p>   |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <p>SEND ALL CORRESPONDENCE TO:<br/>Customer No. 23,115</p>  |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <br><b>SIGNATURE.</b><br>Philippe Y. Riesen  |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <b>NAME</b><br>35,657   |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |
| <b>REGISTRATION NUMBER</b><br>Date: November 3, 2000  |   |                                      |                   |              |      |              |          |   |                  |                    |         |   |                  |   |  |  |                   |                  |

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Akira FUJISHIMA et al.  
Serial No. : Attn: Box PCT  
Filed on :  
Title : Benzimidazole Compound Crystal

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Preliminary to examination please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 1, first sentence, insert "This application is the National Stage of International Application No. PCT/JP00/03881, filed on June 15, 2000."  
Page 3, line 14, delete "includes" and substitute therefor --include--  
Page 3, line 17, delete "method" and substitute therefor --methods--  
Page 4, line 16, delete "an"  
Page 4, line 19, delete "an"  
Page 5, line 10, delete "mixture" and substitute therefor --mixtures--  
Page 5, line 26, delete "Thus" and substitute therefor --A thus--  
Page 6, line 8, delete "more unlikely" and substitute therefor --less likely--  
Page 6, line 11, delete "doses" and substitute therefor --dosage--; after "and" insert -- with a--  
Page 6, line 26, delete "burn" and substitute therefor --burns--  
Page 26, line 24, delete "secretion-inhibit" and substitute therefor --secretion-inhibiting--  
Page 27, line 5, delete "more unlikely" and substitute therefor --less likely--  
Page 27, line 9, delete "doses" and substitute therefor --dosage--; after "and" insert -- with a--

IN THE CLAIMS:

Claim 7, page 28, rewrite the claim to read:

"A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal claimed in Claim 1."

**REMARKS**

The above amendments correct typographical and clerical errors and do not constitute new matter. Entry of the above amendments prior to examination and early action on the merits are respectfully requested.

Date: November 2, 2000

Respectfully submitted,



Philippe Y. Riesen, Reg. No. 35,657  
Attorney for Applicants

Customer No. 23,115

DESCRIPTION

Benzimidazole Compound Crystal

TECHNICAL FIELD

5 The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

BACKGROUND ART

10 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

15 There is a demand for a more stable and excellently absorbable antiulcer agent.

15 DISCLOSURE OF INVENTION

Having chiral sulfur in the molecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

30 [1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;

[2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

35 [3] a crystal according to the above [2] wherein the X-ray

powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;

[4] a pharmaceutical composition which comprises the crystal according to the above [1];

[5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;

[6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;

[7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not. Said "hydrate" includes 0.5 hydrate to 5.0 hydrate.

Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidation to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution includes *per se* known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes *per se* known method.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol,

5        acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

10       The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent 15       moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, an optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] and (-)-menthoxycetic acid; and an optically active alkoxyethyl halides such as 20       (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

25       2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, USP 4,628,098 etc. or analogous methods thereto.

30       Methods of crystallization includes *per se* known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

35       Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.),

halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., 5 acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be 10 used singly or in mixture of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical 15 transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a 20 special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical 25 method, an optical method, etc.

Thus obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, 30 gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its 35 handling is facilitated so that it can be prepared as a solid

pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, 5 the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes more unlikely to be metabolized partly because of the increased protein-binding rate, thus showing an extended 10 duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, 15 rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomach ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* 20 eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from 25 cerebral vascular disorder, head trauma, multiple organ failure and extensive burn necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative 30 stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated 35 with a pharmacologically acceptable carrier, e.g., tablets

(including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release 5 preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire 10 composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human 15 (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier 20 substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for 25 liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, 30 sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

35 Such "binders" include, for example, hydroxypropyl

cellulose, hydroxypropylmethyl cellulose, crystalline cellulose,  $\alpha$ -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic

salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite  
5 [Mg<sub>6</sub>Al<sub>2</sub>(OH)<sub>16</sub>·CO<sub>3</sub>·4H<sub>2</sub>O], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide,  
10 etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example,  
15 polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.  
25

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.  
30

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites,  
35

ascorbic acid and  $\alpha$ -tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

5 Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhettinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

10 Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

15 The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the 20 two layers.

25 For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the 30 present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing 35 triethyl citrate, still further coated with an enteric

coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous 5 enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers [e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), 10 Polykid PA30 (trade name; produced by San-*yo* Chemical)], carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; water-soluble polymers; 15 plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetine and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, multitol, reduced starch saccharides, xylitol, 20 reduced paratinose, erythritol, etc.), crystalline cellulose [e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose · carmellose sodium)], low-substituted hydroxypropyl cellulose [e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu 25 Chemical) and mixtures thereof]; binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

30 The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* 35 action substances, imidazole compounds etc. Such "anti-

"*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., 5 erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem, and so forth. Of these substances, preferred are antibiotic penicillins, 10 antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

15 Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, 20 sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

#### 25 BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the 30 term "room temperature" indicates about 15 to 30 °C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

35  $^1\text{H-NMR}$  spectra were determined with  $\text{CDCl}_3$  as the solvent using Varian Gemini-200; data are shown in chemical shift

$\delta$  (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

5 Optical rotation  $[\alpha]_D$  was determined at 20 °C using the DIP-370 digital polarimeter (produced by JASCO).

10 Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia.  $\times$  250 mm, temperature: about 20 °C, mobile phase: hexane/2-propanol = 80/20 or hexane/2-propanol = 85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

15 Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-K $\alpha$  ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

20 The other symbols used herein have the following definitions:

s : singlet

d : doublet

t : triplet

q : quartet

25 m : multiplet

bs: broad singlet

J : binding constant

### Examples

30 Reference Example 1

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

35 pyridinyl]methyl]sulfinyl]-1H-benzimidazole

(lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.  $\times$  250 mm, temperature: 30 °C, mobile phase: hexane/2-propanol/ethanol = 255/35/10, flow rate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20-25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45  $\mu$ m filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+) -lansoprazole (1.6 g, optical purity > 97.6%ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+) -lansoprazole (1.37 g, optical purity > 99.9%ee) as an amorphous substance.

$$[\alpha]_D = + 174.3^\circ \ (c = 0.994\%, \text{CHCl}_3)$$

Reference Example 2

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+) -lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia.  $\times$  500 mm, temperature: room temperature, mobile phase: hexane/2-propanol = 85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, 1 shot: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45  $\mu$ m filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield

R(+) -lansoprazole (9.31 g, optical purity 98.3%ee) as an amorphous substance.

Reference Example 3

5 Production of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+) -lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55 °C for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55 °C for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5 °C, followed by 3.5 hours of stirring at 0 to 5 °C, to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol = 90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4%ee.

30 Reference Example 4

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+) -lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5

kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60 °C, and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at -5 to 5 °C, followed by 1.5 hours of stirring at -5 to 5 °C, to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/ triethylamine = 50/50/1); adjusted to pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene = 4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35,

3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol = 90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(3) With stirring, a suspension in acetone (20 l) of the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water = 1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol = 90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about

12.5% aqueous ammonia at about 50 °C (23 l) and t-butyl methyl ether at about 50 °C (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water = 1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol = 90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(5) The wet crystal obtained in (4) above was dissolved

in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40 °C, heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40 °C ethyl acetate-heptane (ethyl acetate:heptane = 1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol = 90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

#### Example 1

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept

standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method 5 using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+) -lansoprazole (38 mg).

m.p.: 144.0-144.5 °C (dec.)

10 Elemental analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43,

O: 8.66

Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42

<sup>1</sup>H-NMR: 2.25(3H,s), 4.40(2H,q,J=7.8Hz),

15 4.68(1H,d,J=13.8Hz), 4.85(1H,d,J=13.8Hz),

6.69(1H,d,J=6.0Hz), 7.29-7.39(2H,m), 7.52(1H,m),

7.81(1H,m), 8.37(1H,d,J=6.0Hz), 11.00(1H,bs).

IR(ν cm<sup>-1</sup>): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267,

1163.

20 UVmax(CHCl<sub>3</sub>): 283.7 nm

[α]<sub>D</sub> = + 199.2° (c = 0.202%, CHCl<sub>3</sub>)

Table 1

## Crystal Data and Structure Refinement Parameters

|  |   |  |
|--|---|--|
| Molecular formula                            | : | C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> O <sub>2</sub> F <sub>3</sub> S                                     |
| Molecular weight                             | : | 369.36   |
| Crystal color, habit                         | : | Colorless, tabular   |
| Crystal Dimension                            | : | 0.40 × 0.30 × 0.04 (mm)  |
| Crystal system                               | : | Monoclinic   |
| Lattice constants                            | : | a = 8.549(1) (Å)<br>b = 23.350(1) (Å)<br>c = 8.720(2) (Å)<br>β = 103.90(1) (°)<br>V = 1,689.8(4) (Å <sup>3</sup> ) |
| Space group                                  | : | P <sub>2</sub> 1   |
| Z  | : | 4  |
| Density (calculated)                         | : | 1.452 (g/cm <sup>3</sup> )   |
| Effective reflection number/parameter number | : | 9.12   |
| R (I ≥ 2σ(I))                                | : | 0.036  |
| Flack parameter                              | : | -0.02(2)   |

## 5 Example 2

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

10 Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml), and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure,

15

to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropyl ether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, 20 optical purity 99.8%ee).

m.p.: 147.0-148.0 °C (dec.)

#### Elemental analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66

25 Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22

$^1\text{H-NMR}$ : 2.24(3H,s), 4.38(2H,q,J=7.8Hz),  
4.74(1H,d,J=13.6Hz), 4.87(1H,d,J=13.6Hz),  
6.68(1H,d,J=5.8Hz), 7.26-7.36(2H,m), 7.45(1H,m),  
7.78(1H,m), 8.35(1H,d,J=5.8Hz).

30 IR( $\nu$  cm<sup>-1</sup>): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163

UVmax(CHCl<sub>3</sub>): 283.6 nm

$[\alpha]_D = + 180.3^\circ$  (c = 1.004%, CHCl<sub>3</sub>)

Table 2

## X-ray Powder Diffraction Data

| 2θ (°) | Half-value width | d-value (Å) | Relative intensity (%) |
|--------|------------------|-------------|------------------------|
| 7.560  | 0.141            | 11.6841     | 100                    |
| 13.060 | 0.165            | 6.7733      | 44                     |
| 15.160 | 0.141            | 5.8394      | 55                     |
| 15.440 | 0.141            | 5.7342      | 84                     |
| 20.040 | 0.165            | 4.4271      | 23                     |
| 21.720 | 0.165            | 4.0883      | 89                     |
| 22.560 | 0.141            | 3.9380      | 24                     |
| 22.820 | 0.141            | 3.8937      | 24                     |
| 24.080 | 0.165            | 3.6927      | 37                     |
| 26.120 | 0.118            | 3.4088      | 32                     |
| 28.680 | 0.165            | 3.1100      | 20                     |

## Example 3

5 Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate

10 Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

15 m.p.: 76.0-80.0 °C

20 Elemental analysis

Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13

Found: C: 48.52, H: 4.44, N: 10.49

Table 3

## X-ray Powder Diffraction Data

| 2θ (°) | Half-value width | d-value (Å) | Relative intensity (%) |
|--------|------------------|-------------|------------------------|
| 6.680  | 0.165            | 13.2212     | 9                      |
| 9.200  | 0.165            | 9.6046      | 21                     |
| 9.960  | 0.141            | 8.8734      | 25                     |
| 10.980 | 0.165            | 8.0513      | 42                     |
| 13.380 | 0.141            | 6.6120      | 22                     |
| 14.960 | 0.141            | 5.9170      | 63                     |
| 15.680 | 0.165            | 5.6469      | 100                    |
| 17.640 | 0.212            | 5.0237      | 34                     |
| 19.760 | 0.212            | 4.4892      | 33                     |
| 25.420 | 0.188            | 3.5010      | 23                     |
| 29.800 | 0.188            | 2.9957      | 20                     |

5

## Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23 °C constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M NaHCO<sub>3</sub> and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

10 The results are shown in Table 4.

Table 4

| Sample                   | Dose (mg/kg) | Gastric mucosal injury index (mm) | Suppression rate (%) |
|--------------------------|--------------|-----------------------------------|----------------------|
| Control                  | -            | 10.9 ± 1.9                        | -                    |
| (R)-lansoprazole crystal | 3            | 0.2 ± 0.2*                        | 98.0                 |

15 Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.

\*p < 0.01 (versus control group, Steel's test)

Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60 °C (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions

Detection wavelength : UV 275 nm

Column : YMC Pro C18, 4.6 × 150 mm  
Mobile phase : Fluid prepared by adding phosphoric acid to water/acetonitrile/triethylamine (63:37:1) to reach pH 7.  
Flow rate : 1.0 ml/min  
Column temperature : 40 °C  
Sample injection volume : 10 µl

10 Table 5  
 Stability of R(+)-Lansoprazole Crystal and Amorphous

| Sample    | Duration of storage | Description    | Content (Residual percentage) |
|-----------|---------------------|----------------|-------------------------------|
| Crystal   | 1 week              | Light-brown    | 97.0                          |
|           | 2 weeks             | Brown          | 93.8                          |
|           | 4 weeks             | Brown          | 91.7                          |
| Amorphous | 1 week              | Brown          | 70.8                          |
|           | 2 weeks             | Blackish brown | 57.5                          |

When the sample was stored at 60 °C (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

## INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibit action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In

addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and 5 a greater AUC than the racemate, and becomes more unlikely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and low prevalence 10 of adverse reactions.

## CLAIMS

1. A crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.  
5
2. A crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole.
3. A crystal according to Claim 2 wherein the X-ray powder  
10 diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.
4. A pharmaceutical composition which comprises the  
15 crystal according to Claim 1.
5. A pharmaceutical composition according to Claim 4, which is for treating or preventing digestive ulcer.
6. A method for treating or preventing digestive ulcer in  
20 a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to Claim 1 with a pharmaceutically acceptable excipient, carrier or diluent.
7. Use of the crystal according to Claim 1 for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer.

## ABSTRACT

A novel crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

## Declaration and Power of Attorney for Patent Application

## 特許出願宣言書及び委任状

## Japanese Language Declaration

## 日本語宣言書

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As a below named inventor, I hereby declare that:

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My residence, post office address and citizenship are as stated next to my name.

下記の名称の発明について、特許請求範囲に記載され、且つ特許が求められている発明主題に関して、私は、最初、最先且つ唯一の発明者である（唯一の氏名が記載されている場合）か、或いは最初、最先且つ共同発明者である（複数の氏名が記載されている場合）と信じている。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

## Benzimidazole Compound Crystal

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Prior Foreign Application(s)  
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|                  |                   |                                     |                          |
|------------------|-------------------|-------------------------------------|--------------------------|
| 11-171509        | Japan             | 17/06/1999                          | <input type="checkbox"/> |
| (Number)<br>(番号) | (Country)<br>(国名) | (Day/Month/Year Filed)<br>(出願日／月／年) | <input type="checkbox"/> |
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Priority Not Claimed  
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Attached Sheet to the Declaration

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